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A Clinicohistopathological Study of IgA Nephropathy Associated with Nephrotic Syndrome

Noriaki YORIOKA, Koji WADA, Koji KANAHARA, Takahiko OGAWA, Naoko TAKAHASHI, Hiroaki ODA, Akira HIRABAYASHI, Makoto KOBAYASHI, Sayuri OKUSHIN and Michio YAMAKIDO

The 2nd Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan

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ABSTRACT

Among the 201 cases of IgA nephropathy, a study was made of the clinical characteristics, laboratory findings, and histopathological findings of 11 cases (5.5%) presenting nephrotic syndrome in comparison with those of a non-nephrotic group. The results of this study showed that in comparison with the non-nephrotic group the frequency of hypertension, anemia, and depressed renal function was higher in the nephrotic group and that the histological damage was severer. As can be expected, the frequency of severe proteinuria, hypoproteinemia, and depressed serum IgG value was higher in the nephrotic group, but no significant difference could be demonstrated in degree of hematuria, serum IgA value, and immunofluorescence findings. Furthermore, the response to various treatments was unfavorable and in 3 cases chronic renal failure developed. In general, in many of the cases the prognosis is poor.

On the other hand, the authors experienced one case with minimal change in the histological picture which responded favorably to steroid administration. The significance of such a case is yet unknown.

IgA nephropathy is a primary glomerular disease entity proposed by Berger[4] in 1968. It is usually characterized by microscopic hematuria and slight proteinuria, but in rare cases a clinical picture of nephrotic syndrome is observed. According to earlier reports, cases of nephrotic syndrome in IgA nephropathy are prone to be associated with steroid resistance and renal failure[8,10,12,15]. Recently, a few cases of steroid-sensitive nephrotic syndrome have been reported[2,3,11,13,16].

In the present study, the authors in an attempt to elucidate the clinical specific features of nephrotic syndrome in IgA nephropathy classified IgA nephropathy into nephrotic group and non-nephrotic group and compared the clinical characteristics, laboratory findings, histopathological findings, response to therapy, and outcome of these two groups.

MATERIALS AND METHODS

The subjects of the present study were 201 patients who were diagnosed as IgA nephropathy at the Second Department of Internal Medicine, Hiroshima University School of Medicine between 1982 and 1986 and were composed of 11 nephrotic cases and 190 non-nephrotic cases. Diagnosis of IgA nephropathy was made based on renal biopsy showing dominant mesangial IgA deposition by immunofluorescence method. Cases of systemic lupus erythematosus, purpura nephritis, and hepatic glomerulosclerosis were excluded by clinical history and laboratory tests.

For light microscopic studies, paraffin sections

Table 1. Clinical characteristics and laboratory findings of IgA nephropathy patients with nephrotic syndrome

No.	Case	Sex	Age	Hyper-tension	Gross hematuria	u-RBC/ HPF	TUP g/day	RBC $10^4/mm^3$	Hb g/dl	PLT $10^4/mm^3$
1	M.Y.	F	35	−	+	15-20	3.6	426	11.5	33.5
2	M.N.	F	27	+	+	0- 5	4.4	450	14.1	30.8
3	M.K.	M	28	±	−	5- 7	5.0	509	16.2	20.2
4	S.I.	F	43	±	+	30-40	5.0	409	12.4	23.7
5	M.K.	M	62	±	−	3- 6	6.4	372	12.5	26.9
6	M.N.	F	26	+	−	15-17	4.8	411	11.9	32.0
7	N.O.	F	32	−	+	many	3.6	425	11.3	22.6
8	K.Y.	F	20	−	−	many	4.6	436	12.5	20.2
9	S.F.	F	19	−	−	10-20	3.5	340	10.5	17.9
10	H.Y.	M	47	+	−	0- 5	4.2	270	8.6	22.3
11	M.D.	F	19	±	−	20-30	3.5	396	12.3	29.9

Table 2. Laboratory findings of IgA nephropathy patients with nephrotic syndrome

No.	Case	TP g/dl	TC mg/dl	IgG mg/dl	IgA mg/dl	IgM mg/dl	BUN mg/dl	Cr mg/dl	UA mg/dl	$PSP_{15'}$ %	Ccr ml/min
1	M.Y.	4.8	271	1237	221	384	8.0	0.9	4.0	30.0	68.0
2	M.N.	5.8	285	780	336	121	23.0	1.9	7.3	16.6	37.9
3	M.K.	5.4	174	784	277	145	13.7	1.2	6.3	35.5	67.4
4	S.I.	5.9	171	1173	338	135	28.4	1.9	5.5	38.5	65.0
5	M.K.	5.1	374	1602	876	189	21.1	0.7	5.8	29.0	110.0
6	M.N.	5.3	538	700	253	295	29.0	0.9	5.6	22.0	59.3
7	N.O.	5.5	460	584	165	218	9.5	0.7	3.4	34.0	81.0
8	K.Y.	5.2	272	542	280	211	15.0	0.9	4.7	51.0	82.2
9	S.F.	5.2	396	725	326	259	38.9	2.7	6.7	10.0	29.0
10	H.Y.	5.4	203	1049	190	246	47.0	3.6	9.1	7.0	17.8
11	M.D.	5.8	216	1190	200	45	9.0	1.1	6.5	30.0	76.4

of renal biopsy specimens were stained with HE, PAS, PASM and Masson's trichrome. For immunofluorescence studies, cryostat sections were stained with FITC-conjugated antiserum against human IgG, IgA, IgM, C_3, C_4, and fibrinogen (Hoechst). The specificity of the antisera was tested by immunodiffusion.

Clinical and laboratory data were obtained with respect to sex, age, blood pressure, urinalysis, complete blood count, serum total protein, serum total cholesterol, immunoglobulins, and renal function.

Student's t-test and chi-square test were employed for statistical evaluation of the data.

RESULTS

The clinical characteristics and laboratory findings of the nephrotic patients are summarized in Tables 1 and 2. The results of our comparative studies on the nephrotic and non-nephrotic cases will be described.

1. Clinical characteristics

(1) Sex

The nephrotic group was composed of 3 males and 8 females, while the non-nephrotic group was composed of 110 males and 80 females. The females showed a significantly higher incidence of nephrotic syndrome than the males ($p<0.05$).

(2) Age

The mean age of the nephrotic group was 32.5 ± 13.4 years with age ranging from 19 to 62 years, while that of the non-nephrotic group was 30.6 ± 12.3 years with age ranging from 13 to 64 years. No significant difference in age could be observed between the two groups.

(3) Blood pressure

Hypertension was defined as blood pressure in excess of 140/90 mmHg. Of the 11 nephrotic pa-

tients, 7 had hypertension and of the 190 non-nephrotic cases, 37 showed hypertension. These results show that those belonging to the nephrotic group had a higher incidence of hypertension than that of the non-nephrotic group ($p<0.001$).

(4) Gross hematuria

Of the 11 belonging to the nephrotic group, 4 cases (36.4%) had gross hematuria, but of the 190 belonging to the non-nephrotic group, 51 cases (26.8%) had gross hematuria, but the difference in incidence between the two groups was not significant.

2. Laboratory results

(1) Proteinuria and urinary RBC

The daily urinary protein in all the cases belonging to the nephrotic group exceeded 3.5 g. Their incidence was significantly higher than in the non-nephrotic group ($p<0.001$), having a value of 0 ~ 3.3 g.

Urinary RBC was classified into three groups; slight with the count being under 10/HPF, moderate with the count being from 11 to 100/HPF, and severe with the count being over 101/HPF. In the nephrotic group, 4 cases belonged to the slight group, 5 cases to the moderate group, and 2 cases to the severe group, while in the non-nephrotic group, 115 cases belonged to the slight group, 58 cases to the moderate group, and 17 cases to the severe group. These results indicate that there was no significant difference in urinary RBC between the nephrotic group and non-nephrotic group.

(2) RBC, hemoglobin value and platelet count of the peripheral blood

In the nephrotic group, RBC was 404.0 ± 61.9 × $10^4/mm^3$, hemoglobin value, 12.2 ± 1.9 g/dl, and platelet count, 25.4 ± 5.4 × $10^4/mm^3$, while in the non-nephrotic group, RBC was 458.2 ± 55.5 × $10^4/mm^3$, hemoglobin value, 13.8 ± 1.7 g/dl, and platelet count, 24.9 ± 5.9 × $10^4/mm^3$. These results indicate that RBC and hemoglobin value were significantly depressed in the nephrotic group when compared to those of the non-nephrotic group ($p<0.01$), but no significant difference could be observed between the two group in platelet count.

(3) Serum total protein and total cholesterol

As was expected, serum total protein was less than 6.0 g/dl in all cases belonging to the nephrotic group with the mean being 5.4 ± 0.3 g/dl. These results indicate that in comparison with the non-nephrotic group the serum total protein value was significantly depressed in the nephrotic group ($p<0.001$).

Serum total cholesterol value in the nephrotic group was 305.4 ± 121.4 mg/dl, while that in the non-nephrotic was 193.8 ± 52.8 mg/dl. These results indicated that the serum total cholesterol value in the nephrotic group was significantly elevated when compared to that of the non-nephrotic group ($p<0.001$).

(4) Immunoglobulins

In the nephrotic group, IgG value was 942.4 ± 330.7 mg/dl, IgA value, 314.7 ± 195.6 mg/dl, and IgM value, 204.4 ± 92.9 mg/dl, while in the non-nephrotic group, IgG value was 1355.2 ± 348.3 mg/dl, IgA value, 343.3 ± 140.0 mg/dl, and IgM value, 153.9 ± 82.7 mg/dl. These results show that IgG value in the nephrotic group was significantly depressed when compared to that of the non-nephrotic group ($p<0.001$).

(5) Renal function test

In the nephrotic group, BUN was 22.0 ± 12.8 mg/dl, while in the non-nephrotic group it was 14.2 ± 3.7 mg/dl. Creatinine value in the nephrotic group was 1.5 ± 0.9 mg/dl, while in the non-nephrotic group it was 1.0 ± 0.2 mg/dl. Uric acid was 5.9 ± 1.6 mg/dl in the nephrotic group, while it was 5.5 ± 1.5 mg/dl in the non-nephrotic group.

These results show that BUN and creatinine values in the nephrotic group were significantly elevated when compared to those of the non-nephrotic group ($p<0.001$), but no significant difference was observed in uric acid. Similarly, the 15 min PSP value was 27.6 ± 12.9% in the nephrotic group in contrast to 36.8 ± 11.0% of the non-nephrotic group, while creatinine clearance was 63.1 ± 26.4 ml/min in the nephrotic group and 94.1 ± 26.0 ml/min in the non-nephrotic group. These results indicate that in comparison with the non-nephrotic group the 15 min PSP value was significantly depressed ($p<0.01$) and creatinine clearance was also significantly depressed ($p<0.001$) in the nephrotic group.

3. Histopathological studies

(1) Light microscopic findings

The histological picture in the nephrotic group,

Table 3. Therapy and outcome in IgA nephropathy patients with nephrotic syndrome

No.	Case	Histology	Treatment	Outcome
1	M.Y.	DPGN, moderate	Steroid, Cyclophosphamide	I
2	M.N.	DPGN, advanced	Antiplatelet, Anticoagulant	CRF
3	M.K.	DPGN, moderate	Steroid pulse	II
4	S.I.	DPGN, moderate	Antiplatelet, Anticoagulant	I
5	M.K.	M C	Steroid	CR
6	M.N.	DPGN, moderate	Steroid pulse	II
7	N.O.	DPGN, advanced	Steroid pulse	II
8	K.Y.	DPGN, moderate	Steroid pulse	I
9	S.F.	DPGN, advanced	Anticoagulant	CRF
10	H.Y.	DPGN, advanced	Steroid	CRF
11	M.D.	DPGN, moderate	Anticoagulant	II

CR : Complete remission I : Incomplete remission type I
II : Incomplete remission type II CRF : Chronic renal failure

showed a minimal change in one case (9.1%), diffuse proliferative glomerulonephritis (DPGN) of moderate degree in 6 cases (54.5%), and DPGN of severe degree in 4 cases (36.4%). On the other hand, in the non-nephrotic group, minimal change was observed in 28 cases (14.7%), focal proliferative glomerulonephritis in 14 cases (7.4%), DPGN of mild degree in 39 cases (20.5%), DPGN of moderate degree in 79 cases (41.6%), and DPGN of severe degree in 30 cases (15.8%). These results show that the incidence of cases with severe histological damage was significantly higher in the nephrotic group than in the non-nephrotic group.

(2) Immunofluorescence findings

Study on the frequency of mesangial deposition of IgG, IgM, C_3, C_4, and fibrinogen showed in the nephrotic group one case of IgG (9.1%), 4 cases of IgM (36.4%), 6 cases of C_3 (54.5%), one case of C_4 (9.1%), and one case of fibrinogen (9.1%), while in the non-nephrotic group 18 cases of IgG (9.5%), 32 cases of IgM (16.8%), 139 cases of C_3 (73.2%), 6 cases of C_4 (3.2%), and 58 cases of fibrinogen (30.5%). These results indicate no significant difference in immunofluorescence findings between the nephrotic group and non-nephrotic group.

4. Results of therapy and clinical course (Table 3)

Steroid therapy was conducted on 3 cases, steroid pulse therapy on 4 cases, and anticoagulant therapy on 4 cases, but complete remission was successfully attained in only one case of minimal change with most being progressive cases. Hemodialysis is being given to one case, while 2 cases have developed chronic renal failure.

DISCUSSION

According to the literature, the frequency of IgA nephropathy associated with nephrotic syndrome has been reported to be 6.0% by Clarkson et al[5], 9.6% by Sinniah et al[14], and 11.0% by Hood et al[6] and in Japan 2.3% by Yokoska et al[17], 4.4% by Abe et al[1], 4.5% by Soda et al[15], 6.3% by Yoshida et al[18], and 11.5% by Nakamoto et al[12]. The frequency observed by the present authors is 5.5%, which is in general agreement with those reported by other workers. As for the specific features of IgA nephropathy associated with nephrotic syndrome, it is one of the common clinical characteristics that it is frequently associated with hypertension[1,5,12]. Laboratory findings show that depressed renal function is common[5,6] and it is a common histopathological finding that glomerular and mesangial damages are severe[1,7,14]. As for outcome, it is not uncommon for such cases to develop renal failure[8,10,12,15]. As hardly any studies have been made to examine the statistical difference between the nephrotic group and non-nephrotic group, in this study the authors attempted such a comparison. In our study a significant difference was observed between the nephrotic group and the non-nephrotic group in the clinical features that female sex, hypertension were common, in laboratory findings that anemia, severe pro-

teinuria, hypoproteinemia, elevated total cholesterol, depressed IgG value, and depressed renal function were common, and in histopathological findings that mesangial proliferation was increased. Furthermore, the response to therapy was poor and many cases progressed to renal failure. However, no significant difference could be observed with regard to age, past history of gross hematuria, severity of hematuria, serum IgA value, and frequency of mesangial deposition of IgG, IgM, C_3, C_4, and fibrinogen. These results are in agreement with those published in the literature except for severe proteinuria, hypoproteinemia, hypercholesterolemia, and depressed IgG value derived from nephrotic syndrome. However, it is considered that the sex difference is attributable to chance. It can be concluded from the foregoing results that cases of IgA nephropathy associated with nephrotic syndrome generally show a poor prognosis.

Since the case reported by Mustone et al[11] of complete remission following steroid administration in a case showing minimal change in the histological picture, similar cases have gradually been reported[2,3,9,13,16]. Among our 11 cases of nephrotic syndrome, a similar example was observed in one case. According to Belgiojoso et al[3], Southwest Pediatric Nephrology Study Group[16], the disease entity of such cases is different from the many cases showing poor prognosis. On the other hand, Nakamoto et al[12] have reported that no definite conclusion can yet be obtained, the association of nephrotic syndrome being one of chance. The resolution of this point awaits the analysis of more cases in the future.

REFERENCES

1. **Abe, S., Konishi, K., Kan, K., Kato, E., Amagasaki, Y., Iori, S. and Sakaguchi, H.** 1982. A clinico-pathological study of IgA nephropathy associated with nephrotic syndrome. Kidney and dialysis **13**: 807-812.
2. **Abreo, K. and Wen, S-F.** 1983. A case of IgA nephropathy with an unusual response to corticosteroid and immunosuppressive therapy. Am. J. Kidney Dis. **3**: 54-57.
3. **Belgiojoso, G.B., Mazzucco, G., Casanova,S., Radaelli, L., Monga, G. and Minetti, L.** 1986. Steroid-sensitive nephrotic syndrome with mesangial IgA deposits: a separate entity? Am. J. Nephrol. **6**: 141-145.
4. **Berger, J. and Hinglais, N.** 1968. Les dépôts intercapillaires d'IgA-IgG. J. Urol. Nephrol. **74**: 694-695.
5. **Clarkson, A.R., Seymour, A.E., Thompson, A.J., Haynes, W.D.G., Chan, Y-L. and Jackson, B.** 1977. IgA nephropathy: a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. Clin. Nephrol. **8**: 459-471.
6. **Hood, S.A., Velosa, J.A., Holley, K.E. and Donadio, Jr. J.V.** 1981. IgA-IgG nephropathy: predictive indices of progressive disease. Clin. Nephrol. **16**: 55-62.
7. **Katz, A., Walker, J.F. and Landy, P.J.** 1983. IgA nephritis with nephrotic range proteinuria. Clin. Nephrol. **20**: 67-71.
8. **Kobayashi, Y., Tateno, S., Hiki, Y. and Shigematsu, H.** 1983. IgA nephropathy: prognostic significance of proteinuria and histological alterations. Nephron **34**: 146-153.
9. **Lai, K.N., Lai, F.M., Ho, C.P. and Chan, K.W.** 1986. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin. Nephrol. **26**: 174-180.
10. **Lowance, D.C., Mullins, J.D. and McPhaul, Jr. J.J.** 1973. Immunoglobulin A (IgA) associated glomerulonephritis. Kidney Int. **3**: 167-176.
11. **Mustonen, J., Pasternack, A. and Rantala, I.** 1983. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin. Nephrol. **20**: 172-176.
12. **Nakamoto, Y., Asakura, K., Miki, K., Yasuda, T., Imai, H., Takahashi, H., Enzan, M., Hukuda, S. and Miura, A.** 1985. Nephrotic syndrome associated with IgA nephritis. A reappraisal. Kidney and dialysis **19**: 1293-1299.
13. **Sinnassamy, P. and O'Regan, S.** 1985. Mesangial IgA deposits with steroid responsive nephrotic syndrome: probable minimal lesion nephrosis. Am. J. Kidney Dis. **5**: 267-269.
14. **Sinniah, R., Javier, A.R. and Ku, G.** 1981. The pathology of mesangial IgA nephritis with clinical correlation. Histopathology **5**: 469-490.
15. **Soda, K., Sugawara, M., Nishimura, S., Kohmoto, J., Ogura, T., Mino, Y., Takaoka, M., Hiramatsu, M., Takahashi, K. and Ota, Z.** 1986. Clinico-pathological study of IgA nephropathy with nephrotic syndrome. Jap. J. Nephrol. **28**: 721-728.
16. **Southwest Pediatric nephrology Study Group.** 1985. Association of IgA nephropathy with steroid-responsive nephrotic syndrome. Am. J. Kidney Dis. **5**: 157-164.
17. **Yokoska, H., Nagase, M., Maeda, T. and Koide, K.** 1978. Mesangial IgA glomerulonephritis. Clinicopathological study of 85 cases. Contr. Nephrol. **9**: 101-110.
18. **Yoshida, M., Ebihara, I., Hanzawa, S., Takahashi, T., Koide, H. and Ono, J.** 1980. Clinicopathologic studies of IgA nephropathy associated with nephrotic syndrome. Kidney and dialysis **9**: 353-357.